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14. ABSTRACT

The purpose of the research supported by this IDEA grant award was to test the possibility that variability in the strength of immune surveillance mechanisms against cancer (operationally defined by assessment of natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. The following hypotheses were investigated: Hypothesis 1: Women with family histories of breast cancer are more emotionally distressed than women at normal risk, particularly after notification that they carry a mutation in a primary susceptibility gene. Hypothesis 2: Women with family histories of breast cancer will have lower levels of NK cell activity than normal risk women, which cannot be entirely attributed to the effects of higher emotional distress or the presence of a mutation in primary susceptibility genes. Hypothesis 3: Variability in NK cell activity will contribute to variability in the penetrance of mutations in primary susceptibility genes for breast cancer. Data has been collected on 255 women. Preliminary analyses support these hypotheses.

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Breast Cancer

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INTRODUCTION:

The penetrance of mutations in primary breast cancer susceptibility genes (BRCA1/BRCA2) is highly variable. The mechanisms underlying this variability are not yet well established (Dite et al., 2000; Antoniou et al., 2002; Couch, 2004). Modifying genes and/or environmental factors are likely to play a major role (Antoniou et al., 2002; Couch, 2004). To date, the search for such factors has primarily focused on hormonal/reproductive variables previously established as independent risk factors for breast cancer (DeJong et al., 2002; Martin & Weber, 2000). Another factor that could contribute to differences in penetrance, and/or make an independent contribution to risk is variability in immune surveillance. One immune surveillance mechanism (natural killer cell activity, NKCA) has been reported to be lower in women with family histories of breast cancer, consistent with inherited deficits in immune surveillance (Bovbjerg & Valdimarsdottir, 2001). However, the lower levels of NKCA in these women could be secondary to higher levels of stress, to which NCKA is particularly sensitive **(**Segerstrom & Miller, 2004). Consistent with this possible environmental effect on NKCA, survey studies have found higher levels of distress among women with family histories of breast cancer (Bovbjerg & Valdimarsdottir, 2001; Lindberg & Wellisch, 2004; Schnur et al., 2004, Kim et al., 2005).

The purpose of the research supported by this IDEA grant award was to test the possibility that differences in the strength of immune surveillance mechanisms against cancer (operationally defined as natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. The first aim was to investigate two possible explanations for variability in NKCA (Bovbjerg & Valdimarsdottir, 2001): 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. The second aim was to examine the possibility that inherited deficits in immune surveillance may be independently associated with familial risk of breast cancer (Bovbjerg & Valdimarsdottir, 2001).

The study "piggy-backed" on other studies involving familial risk, genetic counseling, and breast cancer gene testing (BRCA1, BRCA2) under the direction of Co-Investigators on this proposal. These “parent” studies, which provided the infrastructure and funding necessary for recruitment, assessment, genetic counseling, and BRCA testing, were the source of potential participants for the present study. The participants in the present study were recruited to form three Study Groups (N=80/group) of comparable age for the research: 1) The Mutation-Positive Family History Group (Mut+Hist+) includes women whose family histories of cancer indicate a relative risk $\geq$ 1.5 for breast cancer and who carry a mutation in BRCA1 or BRCA2; 2) The Mutation-Negative Risk Family History Group (Mut-Hist+) includes women with comparable family histories, who do not carry mutations; 3) The Normal Risk Group (Mut-Hist-) includes women without family histories of cancer who do not carry mutations. Study participants completed psychological assessments (e.g., standardized self-report measures) in conjunction with their involvement with the parent studies that fund the genetic testing. To reduce participant burden and avoid compromising the parent studies, blood samples for the assessment of NKCA were also collected in conjunction with the women’s involvement in the parent studies, by collecting additional samples when the women were already providing a sample for genetic testing. In the context of the requirements of the parent studies, it has not been feasible to collect blood samples for the two follow-up NK cell assessments originally proposed for this study, as psychological data is collected by telephone. Consistent with scheduling exigencies, NKCA was concurrently assessed in samples from women in each group by personnel "blind" to group status.

BODY:
In the first year of the grant, Bovbjerg (PI) and Valdimarsdottir (Co-I) moved from Memorial Sloan-Kettering Cancer Center to Mount Sinai Medical Center. The resulting site change required modification of collaborative arrangements (e.g., the addition of Eng as a co-investigator), set up of new facilities (e.g., Bovbjerg lab), hiring of new support staff, and additional attention to institutional review requirements. Subsequent to that change, Eng left Mount Sinai and Valdimarsdottir began a new collaborative study involving investigators at another institution (Georgetown) necessitating further modification of collaborative arrangements. These complications caused a delay in the proposed rate of study accrual and the necessity of applying for several no-cost extensions.

In 2002, we proposed three methodological changes to expedite the meeting of our study goals in light of the delays: 1) we reduced the sample size to 80 per group from 100; 2) we modified the scheduling of assessments to enhance recruitment efforts; 3) we streamlined the immune assessments by using well validated and reliable whole blood approaches (e.g., four color flow cytometry), rather than approaches requiring labor intensive isolation of peripheral blood lymphocytes. In 2003, we proposed an additional change based on our experience in recruiting for the study: we reduced the sample size for the assessments of NK cell activity to 140.

Our progress according to the original Statement of Work is detailed below:

Task 1: Preparation for first wave of subjects. Preparation of psychosocial questionnaires and immune assessments. Data base established.

Completed, as previously reported.

Task 2: First wave of subjects completes assessments. Data entry and initial analysis.

Completed, as previously reported.

Task 3: Complete data entry of first wave. Prepare annual report. Prepare for second wave of subjects.

Completed, as previously reported.

Task 4: Second wave of subjects completes assessments. Data entry and analyses continues.

Completed, as previously reported.

Task 5: Complete data entry of first wave. Prepare annual report. Prepare for second wave of subjects.

Completed, as previously reported.

Task 6: Third wave of subjects completes assessments. Data entry and analyses continues.

Completed.

Task 7: Complete data entry for third wave. Complete empiric risk determination. Verify study data. Conduct literature review of relevant articles. Meet with research team to review results. Complete statistical analyses. Write manuscripts; prepare graphics. Complete DOD final report.

Completed. Preliminary analyses are completed. Further analysis of data will continue with funding from other sources.

Throughout the grant period we have made consistent progress toward our study goals and have completed recruitment. Over the grant period a total of 255 women (Mut+Hist+ n=99; Mut-Hist+ n=80; Mut-Hist- n=76) have completed psychological assessments (Assessment 1: n=255; Assessment 2: n=182; Assessment 3: n=142). Over the grant period NK cell activity has been assessed in a total of 135 women (Mut+Hist+ n=37; Mut-Hist+ n=45; Mut-Hist- n= 53).

Analyses thus far have supported our hypotheses:

- Hypothesis 1: Women with family histories of breast cancer will be more emotionally distressed than women at normal risk, particularly after notification that they carry a mutation in a primary susceptibility gene.
    - Healthy women undergoing genetic testing for BRCA mutations, compared to controls, before and after testing have higher levels of:
        - Perceived risk of the disease
        - Breast cancer-specific distress (intrusion/avoidance)
        - Anxiety symptoms
        - Depressive symptoms
    - Women post negative BRCA result have:
        - Reduced perceived risk
        - Reduced breast cancer-specific distress, anxiety/depressive symptoms
    - Women post positive BRCA result have:
        - Increased perceived risk
        - Increased breast cancer-specific avoidance
        - No change in breast cancer-specific intrusions, or anxiety/depressive symptoms
        - Remain higher than controls on all

- Hypothesis 2: Women with family histories of breast cancer will have lower levels of NK cell activity than normal risk women, which cannot be entirely attributed to the effects of higher emotional distress or the presence of a mutation in primary susceptibility genes.
    - Analyses have not yet been completed.

- Hypothesis 3: Variability in NK cell activity will contribute to variability in the penetrance of mutations in primary susceptibility genes for breast cancer.
    - Analyses have not yet been completed.

KEY RESEARCH ACCOMPLISHMENTS:

Accepted abstracts:

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Zakowski SG, Valdimarsdottir HB, Bovbjerg DH. Cancer-specific distress and reduced NKCA in women at familial risk for breast cancer: the buffering role of emotional expressivity. Psychoneuroimmunology Research Society May 2001.

Kim Y, Valdimarsdottir H, Bovbjerg DH. Coping strategies as moderators of cancer-specific distress among healthy women with family histories of breast cancer. Psychosomatic Medicine 2002; 64:106.

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Erblich J, Bovbjerg DH, Valdimarsdottir HB. Looking forward and back: distress among women at familial risk for breast cancer. Annals of Behavioral Medicine 2000; 22:53-59.

Erblich J, Bovbjerg DH, Norman C, Valdimarsdottir HB, Montgomery GH. It won't happen to me: Lower perception of heart disease risk among women with family histories of breast cancer. Preventive Medicine 2000; 31:714-721.

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Thompson HS, Valdimarsdottir HB, Buteau-Buck C, Guevarra J, Bovbjerg DH, Richmond-Avellaneda C, Godfrey D, Brown K, Offit K. Psychosocial predictors of BRCA counseling and testing decisions among urban African-American women. Cancer Epidemiology, Biomarkers & Prevention 2002; 11:1579-1585.

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Dettenborn L, James GD, van Berge-Landry H, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH. Heightened cortisol responses to daily stress in working women at familial risk for breast cancer. Biological Psychology 2005; 69:167-179.

Guevarra JS, Kwate NA, Tang TS, Valdimarsdottir HB, Freeman HP, Bovbjerg DH. Acculturation and its relationship to smoking and breast self-examination frequency in African American women. Journal of Behavioral Medicine 2005; 28:191-201.

Rowe JL, Montgomery GH, Duberstein PR, Bovbjerg DH. Health locus of control and perceived risk for breast cancer in healthy women. Behavioral Medicine 2005; 31(1):33-40.

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DiLorenzo TA, Schnur J, Montgomery GH, Erblich J, Winkel G, Bovbjerg DH. A model of disease-specific worry in heritable disease: The influence of family history, perceived risk and worry about other illnesses. Journal of Behavioral Medicine in press.

REPORTABLE OUTCOMES:
Funded grants:

Department of the Army 7/1/01 - 6/30/05
(Bovbjerg, PI)
(Valdimarsdottir, Project 2 PI)
(Brown, McGovern, Co-Inv)

Center Grant: Genetic Factors in Breast Cancer: Center for Interdisciplinary Biobehavioral Research: Project 2: "Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA decision making among women with breast cancer"(Valdimarsdottir, PI)

National Cancer Institute 12/1/02 - 11/30/07
(Valdimarsdottir, PI)
(Bovbjerg, Co-Inv)

Decisions & Outcomes of BRCA 1/2 Test for Breast Patients

American Cancer Society 1/1/03 - 12/31/06
(Valdimarsdottir, PI)
(Bovbjerg, Co-Inv)

BRCA Counseling/Testing for Urban African American Women

Department of the Army 7/1/02 - 6/30/07
(Bovbjerg, PI)

Immune Surveillance, Cytokines and Breast Cancer Risk: Genetic and Psychological Influences in African American Women

Department of the Army 06/01/04-05/30/08
(Valdimarsdottir, PI)
(Bovbjerg, Co-Inv)

Emotional, Biological and Cognitive Impact of a Brief Expressive Writing Intervention for African American Women at Familial Breast Cancer Risk

Invited Lectures/Presentations:
Biobehavioral consequences of stress in individuals. Danish Cancer Society, Copenhagen, Denmark, 1998.

Psychoneuroimmunology and cancer. University of Aarhus, Aarhus, Denmark, 1998.

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Increased psychobiological stress responses in healthy women at familial risk for breast cancer. Georgetown University, Washington, DC, 2004.

Familial breast cancer risk: a biobehavioral analysis. Long Island University, Brooklyn, NY, 2004.

Familial breast cancer risk: a biobehavioral analysis. Ohio State University, Columbus, OH, 2004.

Psychobiological processes in familial breast cancer risk. Fred Hutchinson Cancer Research Center, Seattle, Washington, 2005.

CONCLUSIONS:

At the conclusion of our final grant year, we have collected psychological data on 255 women and immune data on 135 women. As our preliminary analyses has revealed, the results of the research are consistent with the hypothesis that deficits in immune surveillance (e.g., as a result of stress) moderate the effects of mutations in primary susceptibility genes, the study could have important implications for the eradication of breast cancer. These results raise the possibility that appropriate interventions to reduce stress and increase the activity of immune surveillance mechanisms in women carrying mutations in primary susceptibility genes might delay the onset or prevent the development of breast cancer. In addition, this IDEA award has indirectly led to

the funding of five additional grants to study familial breast cancer risk, publication of 31 abstracts and articles by the investigators, and 18 invited presentations by the PI, thus establishing the team as leaders in the field of research on familial risk for breast cancer.

PERSONNEL:

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